

AMENDMENTS TO THE CLAIMS

Pursuant to 37 C.F.R. §1.121 the following is a complete listing of the claims of the present application. Please cancel claims 1-11 and 14-21 as being drawn to non-elected subject matter. With the foregoing amendments to the claims, the following listing of claims will replace all prior versions, and listings, of claims in the application:

Claims 1-11 (Canceled)

12. (Original) A method of treatment for hereditary lymphedema, comprising the step of administering to a patient with hereditary lymphedema a therapeutically effective amount of a growth factor product selected from the group consisting of vascular endothelial growth factor C (VEGF-C) protein products, vascular endothelial growth factor D (VEGF-D) protein products, VEGF-C gene therapy products, and VEGF-D gene therapy protein products.

13. (Original) A therapeutic or prophylactic method of treating lymphedema, comprising the steps of:

providing isolated lymphatic endothelial cells or lymphatic endothelial progenitor cells;

transforming or transfecting the cells ex vivo with a polynucleotide comprising a nucleotide sequence that encodes a wild type VEGFR-3;

and administering the transformed or transfected cells to the mammalian subject.

Claims 14-21 (Canceled)

22. (Original) A purified polynucleotide comprising a nucleotide sequence encoding a human VEGFR-3 protein variant; wherein said polynucleotide is capable of hybridizing to the complement of SEQ ID NO: 1 under the following hybridization conditions:

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hybridization at 42°C in 50% formamide, 5X SSC, 20 mM Na•PO4, pH 6.8;
and

washing in 0.2X SSC at 55°C;

and wherein the encoded VEGFR-3 protein variant has an amino acid sequence that differs from the amino acid sequence set forth in SEQ ID NO: 2 at one or more positions selected from the group consisting of amino acids 843 to 943 of SEQ ID NO: 2 and amino acids 1009 to 1165 of SEQ ID NO: 2.

23. (Original) A purified polynucleotide according to claim 22, wherein the encoded VEGFR-3 protein variant has an amino acid sequence that differs at position 1114 from the amino acid sequence set forth in SEQ ID NO: 2.

24. (Original) A purified polynucleotide according to claim 22 wherein the encoded VEGFR-3 protein variant has an amino acid sequence that differs from the amino acid sequence set forth in SEQ ID NO: 2 at position selected from the group consisting of residues 857, 1041, 1044 and 1049 of SEQ ID NO: 2.

25. (Original) A purified polynucleotide comprising a nucleotide sequence encoding a VEGFR-3 protein of a human that is affected with heritable lymphedema;

wherein said polynucleotide is capable of hybridizing to the complement of SEQ ID NO: 1 under the following hybridization conditions: hybridization at 42°C in 50% formamide, 5X SSC, 20 mM Na•PO4, pH 6.8; and washing in 0.2X SSC at 55°C;

and wherein the polynucleotide encodes a VEGFR-3 amino acid sequence that differs from SEQ ID NO: 2 at at least one residue.

26. (Original) A purified polynucleotide according to claim 25 wherein the polynucleotide encodes an amino acid sequence that differs from SEQ ID NO: 2 at at least one residue selected from the group consisting of residues 843 to 943 and 1009 to 1165 of SEQ ID NO: 2.

27. (Original) A vector comprising a polynucleotide according to claim 25.

28. (Original) A host cell that has been transformed or transfected with a polynucleotide according to claim 25 and that expresses the VEGFR-3 protein encoded by the polynucleotide.

29. (Original) A host cell according to claim 28 that has been co-transfected with a polynucleotide encoding the VEGFR-3 amino acid sequence set forth in SEQ ID NO: 2 and that expresses the VEGFR-3 protein having the amino acid sequence set forth in SEQ ID NO: 2.

30. (Original) A method for identifying a modulator of intracellular VEGFR-3 signaling, comprising the steps of:

- a) contacting a cell expressing at least one mutant mammalian VEGFR-3 polypeptide in the presence and in the absence of a putative modulator compound;
- b) detecting VEGFR-3 signaling in the cell; and
- c) identifying a putative modulator compound in view of decreased or increased signaling in the presence of the putative modulator, as compared to signaling in the absence of the putative modulator.

31. (Original) A method according to claim 30 wherein the cell expresses the mutant mammalian VEGFR-3 polypeptide and a wildtype mammalian VEGFR-3 polypeptide.

32. (Original) A method according to claim 31 wherein the mutant and wildtype VEGFR-3 polypeptides are human.

33. (Original) A method according to claim 32 wherein said mutant VEGFR-3 polypeptide is characterized by a substitution or deletion mutation in a kinase domain of the VEGFR-3 polypeptide.

34. (Original) A method according to claim 32 wherein said mutant VEGFR-3 polypeptide is characterized by at least one substitution or deletion of the wild type VEGFR-3 amino acid sequence set forth in SEQ ID NO: 2, said at least one substitution or deletion occurring at a position corresponding to a residue selected from positions 843 to 943 and positions 1009 to 1165 of SEQ ID NO: 2.

35. (Original) A method according to claim 32 wherein the mutant VEGFR-3 polypeptide comprises a leucine amino acid at the position corresponding to position 1114 of SEQ ID NO: 2.

36. (Original) A method according to claim 32 wherein said mutant VEGFR-3 polypeptide is characterized by at least one substitution or deletion of the wild type VEGFR-3 amino acid sequence set forth in SEQ ID NO: 2, said at least one substitution or deletion occurring at a position corresponding to a residue selected from positions 857, 1041, 1044 and 1049, and 1114 of SEQ ID NO: 2.

37. (New) The method of claim 12, wherein said patient with hereditary lymphedema comprises a mutation that alters the encoded amino acid sequence of at least one VEGFR 3 allele of the patient wherein said mutation reduces ligand-mediated signaling of the VEGFR-3 polypeptide encoded by the allele, when compared to VEGFR-3 encoded by a wild-type human VEGFR-3 allele.

38. (New) The method of claim 37, wherein said mutation is a mutation altering a tyrosine kinase domain amino acid sequence of the protein encoded by the VEGFR-3 allele.

39. (New) The method of claim 37 wherein said mutation is a missense mutation in a VEGFR-3 allele at a position corresponding to one of codons 857, 1041, 1044 and 1049 of the VEGFR-3-encoding sequence set forth in SEQ ID NO:1.

40. (New) The method of claim 37 wherein said mutation is a missense mutation in a VEGFR-3 allele at a position corresponding to codon 1114 of the VEGFR-3-encoding sequence set forth in SEQ ID NO:1.

41. (New) The method of claim 37, wherein the wildtype VEGFR-3 allele comprises the VEGFR-3 coding sequence set forth in SEQ ID NO: 1.

42. (New) The method of claim 12, wherein said administering of said therapeutically effective amount of said growth factor product induces VEGFR-3 signaling in the lymphatic endothelia of affected individuals.

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43. (New) The method of claim 12, wherein said administering of said therapeutically effective amount of said growth factor product induces VEGFR-3 signaling in the lymphatic endothelia of affected individuals.

44. (New) The method of claim 12, wherein said administering of said therapeutically effective amount of said growth factor product reduces edema in the limbs of said patient.

45. (New) The method of claim 12, wherein said administering of said therapeutically effective amount of said growth factor product reduces accumulation of lymph fluids in said patient.

46. (New) The method of claim 12, wherein said therapeutically effective amount of said growth factor product is administered locally at the site of said edema.

47. (New) The method of claim 12, wherein said growth factor product is VEGF-C.

48. (New) The method of claim 47, wherein said VEGF-C is a mutant VEGF-C.

49. (New) The method of claim 48, wherein said mutant VEGF-C is a VEGF-
C Δ C₁₅₆.

50. (New) The method of claim 47, wherein said VEGF-C is administered via intravenous injection.

51. (New) The method of claim 47, wherein said VEGF-C is administered via intramuscular injection.